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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 08/704,159      | 08/28/1996  | JAMES A. WILLIAMS    | OPHD-02304          | 8816             |

33197 7590 07/02/2003

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EXAMINER

LI, BAO Q

| ART UNIT | PAPER NUMBER |
|----------|--------------|
| 1648     | 50           |

DATE MAILED: 07/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

|                              |                        |                  |
|------------------------------|------------------------|------------------|
| <b>Office Action Summary</b> | Application No.        | Applicant(s)     |
|                              | 08/704,159             | WILLIAMS ET AL.  |
|                              | Examiner<br>Bao Qun Li | Art Unit<br>1648 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 21 April 2003.

2a) This action is **FINAL**.      2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 113-134 is/are pending in the application.

4a) Of the above claim(s) 126-134 is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 113-125 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some \* c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

#### Attachment(s)

1) Notice of References Cited (PTO-892)      4) Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)      5) Notice of Informal Patent Application (PTO-152)

3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_ .      6) Other: \_\_\_\_\_.

### **DETAILED ACTION**

Amendment I, paper No. 46 filed on December 12 is acknowledged. Claims 42-43, 54-57, 64-65, 79, 83, 86, 89-94, 97, 100 and 103-112 have been canceled. New claims 113-134 have been added.

And amendment J, paper No. 49 filed on April 21, 2003 is acknowledged. Claims 113 and 132 have been amended.

Claims 113-134 are pending.

#### *Election/Restrictions*

1. Applicant's election with traverse of Group II, claims 113-115, 117-119 and 122-125 within the scope of botulinum toxin serotype A and SEQ ID NO: 27 in Paper No. 49 is acknowledged. The traversal is on the ground(s) that the pending claims 113-134 are all related to methods for producing recombinant botulinum toxin using prokaryotic expression systems. Therefore, the restriction requirement should be withdrawn.
2. Applicants' argument has been respectfully considered; claims 120-121 and 122-125 are rejoined with the elected group II. However, claims 126-134 are not rejoined with elected group II because they are directed to use different method for producing the soluble botulinum toxin by using a different approach rather than to use a weak promoter only. They are methods distinct from the claimed method in the group II.
3. Regarding to the specific election, Applicants argue that searching all listed sequences would not impose a serious unique burden on the examiner because they are all highly conserved domain of botulinum toxin types.
4. Applicants' argument has been fully considered; however, it is not found persuasive because each serotype of botulinum toxin have different structurally different sequence and each of them required separate search both in house and in the commercial data base. The source for searching structurally different sequences is rather limited in the office. The specific election is proper, which gives Applicants enough embodiment protection for the claimed sequences unless the claimed method for making the polypeptide encoded by a sequence is obvious or known in the art. Therefore, the species election is made Final.

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5. Claims 113-124 in the scope of serotype A and SEQ ID NO: 27 are considered. Because claim 125 is not directed to the elected sequence of SESID NO 27, it is not considered.
6. Applicants are reminded to amend the claims in the scope of serotype A and SEQ ID NO: 27 for reflecting the examination on the merits.
7. Applicants are reminded to cancel the claims 125-134 drawn to the non-elected group.

***RCE***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/16/2003 has been entered and the RCE action follows.

***Claim Rejections - 35 USC § 112***

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:  
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
9. Claims 113-125 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
10. Claim 113 is indefinite in that the metes and bounds of "a weak promoter" are not defined. The claim is interpreted in light of the specification; however, the specification does not teach what the definition of "a weak promoter" is. If Applicants wish to claim a particular promoter, please amend claim to the specific promoter(s). This affects the dependent claim 114-125.
11. Claims 113-125 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP

§ 2172.01. The omitted steps are: the culture condition, such as inducing time and temperature, and a step of purification etc.

***Claim Rejections - 35 USC § 112***

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 113-114, 116, 119 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for having a method for producing a soluble recombinant botulinum toxin serotype A by using a vector pHsBot with a promoter T7lac or lacTq T7lac of lacIq T7 in a host cell BL21, does not reasonably provide enablement for having a method for producing a soluble recombinant botulinum toxin with any weak promoter in any host cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

14. The test of scope of the enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art would undue experimentation (See United States v. Theketronic Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighting many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *gair in re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988). These factors include the following:

15. 1) & 2). State of art and unpredictability of the field.

16. The method of producing recombinant protein by using prokaryotic expression vector is known in the art. However, it is unpredictable that the expressed protein is always a soluble one. The solubility of an expressed protein depends on many factors, such as the construct of the protein, the size of the protein, the host cell, the vector used, the promoter used and the condition of fusion protein inducting time and/or temperature etc. For example, LaPenotiere et al. (Toxin 1995, Vol. 33, pp. 1383-1386) expressed recombinant botulinum by using a prokaryotic vector

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pMAL-p with a lac promoter but in E coil K12 DH5 $\alpha$  host cells, they found that most recombinant fusion proteins were expressed in an insoluble fraction (See last section on page 1386).

17. 3) & 4) Number of working examples and Amount of guidance presented in the specification.

18. Specification only presents that vector pHisBot with a promoter T7lac or lacTq T7lac of lacIq T7 in a host cell BL21 is able to express botulinum toxin as a soluble protein; however, it teach any prokaryotic vector rather any host cell will be able to express the botulinum toxin as a soluble protein. Applicants do not provide adequate guidance for a skilled artisan to select a prokaryotic vector with any or all weak promoter to produce the botulinum toxin as a soluble one.

19. 5) Scope of the claims.

20. The claims broadly read on a method for producing a soluble botulinum toxin with any prokaryotic vector with any weak promoter.

21. 6) & 7) Nature of the invention and lever of the skill in the art.

22. The invention involves to the filed of express a protein as a soluble by using recombinant DNA technology. Although the general technology is known in the art, however, to select a suitable vector and promoter as well as working condition require high level of knowledge of molecular biology at the PhD level to do lot of excessive experiment with unpredicted result.

23. Given the above analysis of the factors, which the courts have determined, are critical in asserting whether a claimed invention is enabled, it must be considered that the skilled artisan would have to conduct undue and excessive experimentation in order to practice the claimed invention.

### ***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 703-305-1695. The examiner can normally be reached on 7:00 to 4:00.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Bao Qun Li

  
June 26, 2003